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Sources of Infection in Childhood Tuberculosis in a Region of East Croatia

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A B S T R A C T

Possible sources of tuberculosis (TBC) infection in children have been assessed in a retrospective epidemiological study covering a north-east region of Croatia in which the incidence of childhood tuberculosis has been increasing since the war in 1991–1995. During the past decade (1993–2003), 271 children up to 18 years of age have been referred for hospital care because of known contacts with tuberculosis (142 children, group A) or because of indicative clinical signs and symptoms (129 children, group B). Possible sources of infection were identified on the basis of medical documentation and field investigations. Frequencies of source identification for different age groups were compared. In group A, the exposure took place most often within the family (parents, grandparents, siblings, 129 of 142 children, 90.8%). Relatives, neighbors, friends and schoolmates accounted for 9.2%. In group B, possible sources of infection were identified for 44 of 129 children (34.1%) and were within the family for 16 of those 44 (36.4%). Evidenced contact with tuberculosis was more usual among younger children (0–9 years of age, 65.5%) in group A than among the older ones (10–18 years of age, 34.5%). In group B, contacts with tuberculosis were equally distributed (50.0%) among younger and older children. High proportion of unrecognized contacts in children having clinical signs and symptoms indicative of tuberculosis (group B, 85 of 129, 65.9%) opens the possibility that extra-familial exposure to tuberculosis occurs more often than expected regardless of the age of children.

Key words: *tuberculosis, child, infection, epidemiology, family, war, PPD, skin test*

Introduction

The incidence of childhood tuberculosis has been rising in many parts of the world and the risk factors vary by region[1–3]. Croatia is among European countries with the highest prevalence of tuberculosis[4]. Croatian incidence was 79 per 100,000 inhabitants in 1983, 46 in 1992 and 34 in 2002[4]. Brodsko-Posavska county (a north-east region of Croatia, in which the present study was carried out) has experienced an increase of tuberculosis during the past decade and now is among the regions with the highest incidence of tuberculosis in Croatia, 49.2 per 100,000[4]. The same applies for childhood tuberculosis. Recent data show an incidence of 18.1 per 100.000 children 0–4 years of age and 17.3, 24.7 and 15.6, respectively, in children 5–9, 10–14 and 15–19 years of age[4]. Previous communication (N. Aberle et al, in press) ascribes that situation to the involvement of Brodsko-Posavska county in military activities in the period from 1991 to 1993, to migrations of displaced people until 1995 and to a deterioration of economy.

Tuberculosis in children is an indicator of its prevalence in community. Detection of a child with tuberculosis, or a child whose tuberculin skin test indicated recent exposure to infection, alerts physician to look for possible contacts. In addition, infected children are at risk of developing tuberculosis later in life.

During the past decade (1993–2003) 271 children were referred to our pediatric pulmonary service for evaluation of tuberculosis either because of known contact with persons having (or having had) tuberculosis or because of suspectful clinical signs and symptoms. This article summarizes our experience with regard to presumed sources of infection.

Patients and Methods

This study involved 271 children up to 18 years of age referred during the past decade (1993–2003) to the

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Pulmonary Service of the Children's Department of the Slavonski Brod General Hospital by the primary care pediatricians or family practitioners because of known contact with tuberculosis (142 children, group A) or because of indicative clinical signs and symptoms such as persistent dry cough, respiratory infection, skin test conversion, cervical lymphadenopathy, recurrent fever or unexplained poor general condition (129 children, group B). Quite often the signs and symptoms were also present in group A, e.g. persistent cough or skin test conversion.

There were 68 girls and 75 boys in group A and 68 girls and 60 boys in group B (χ^2=0.839, df =1, p=0.359). Children in group A were 0.1–18 years of age (median 10 years, X±SD= 9.6±4.3 years) and children in group B were 1 to 18 years of age (median 7 years, X±SD=7.7±4.1 years). The difference is statistically significant at p<0.001.

Diagnostic procedures included PPD skin testing, chest X-ray, chest CT scan (in selected cases) routine laboratory analyses of blood, serum and urine, analysis of the cerebrospinal fluid (if needed), spirometry (in children older than 6 years) bronchoscopy (as indicated), and bacteriological examination for *M. tuberculosis.* Depending on the age and compliance of the children, expectorates or gastric lavages were cultured. Four and sometimes six samples were collected early in the morning before meal. Löwenstein-Jensen or MGIT cultures were employed and in selected cases PCR was done. Cerebrospinal liquor or urine were cultured in cases of meningitis and renal tuberculosis.

Diagnosis of tuberculosis in children is often difficult because of the lack of specific symptoms, and more than 50% of afected children may be asymptomatic[2,3,5]. Bacteriological diagnosis is limited due to difficulties in obtaining sputum from small children. Epidemiological evidence of exposure to a person having tuberculosis is therefore essenial for the diagnosis of tuberculosis in children. Epidemiological data, positive PPD test and chest X-ray form the basis for distinction between recent infection (without disease) and infection with disease. Preventive or a curative treatment is instituted accordingly.

Skin tests were performed (as required in our country) with 2 units of PPD (Statens Serum Institut, Denmark). The readings were classified as negative (<5 mm), indeterminate (6–15 mm) or positive (≥15 mm). Conversion is defined as a positive skin test in a child who has had an indeterminate or negative skin test at a previous screening and became positive without revaccination, or has been found positive two or more years after the revaccination[6]. It should be noted that BCG vaccination is mandatory in Croatia and 97% children receive it. The vaccine is given in the neonatal period and repeated if the systematic skin tests with PPD at 1, 8 or 12–14 years of age are negative. Conversion of a negative (0–5 mm) or indeterminate skin test (6–10 mm) to positivity (>15 mm) without revaccination is considered to indicate recent exposure[6].

Diagnostic categories were: exposure, infection, primary lung tuberculosis, early and late postprimary tuberculosis. Commonly accepted diagnostic criteria were observed[2,3,5].

For each child a thorough epidemiological survey was carried out together with the epidemiological service of the county. The search included interviews with presumed contacts, examination of available medical documentation and screening of suspected contacts by means of chest X-rays and microbiological tests. Individuals having clinically verified tuberculosis and positive bacteriological cultures for M. tuberculosis have been considered s*ources of infection*, individuals having had clinically verified tuberculosis but negative sputum were *potential source of infection*, and *case contacts* were persons who had had tuberculosis before the propositus. For the purpose of this report, exposure of the child to any of these presumable sources were termed *contacts*.

The results were statistically evaluated by means of the Student's t-test or the χ^2-test, as appropriate. The level of significance was set at $p < 0.05$.

Results

Discharge diagnoses for 271 admitted children were as follows: exposure/contact 46 children (16.9%), latent infection 108 (40.1%), specific hilar lymphadenopathy

TABLE 1
POSSIBLE SOURCES OF INFECTION FOR CHILDREN ADMITTED BECAUSE OF KNOWN EXPOSURE TO TUBERCULOSIS (GROUP A)

Source	Years of age				
	0–4	5–9	10–14	15–19	All
Father, mother, or both	23	31	20	6	80
Grandfather, grandmother, or both	12	19	11	3	45
Siblings	0	2	2	0	4
Relatives	2	3	6	0	11
Neighbours, friends	0	1	0	0	1
Schoolmates	0	0	1	0	1
Total	37	56	40	9	142

χ^2=11.272, df=15, p=0.733

TABLE 2
POSSIBLE SOURCES OF INFECTION FOR CHILDREN ADMITTED BECAUSE OF CLINICAL SIGNS AND SYMPTOMS COMPATIBLE WITH TUBERCULOSIS (GROUP B)

Source	Years of age				
	0–4	5–9	10–14	15–19	All
Father, mother, or both	1	0	3	1	5
Grandfather, grandmother, or both	3	4	3	0	10
Siblings	0	1	0	0	1
Relatives	2	3	4	1	10
Neighbours, friends	4	4	5	3	16
Schoolmates	0	0	2	0	2
Total identified	10	12	17	5	44
Not identified	14	21	40	10	85
All	24	33	57	15	129

χ^2=11.440, df=15, p=0.771

TABLE 3
INTRA-FAMILIAL CONTACTS WITH TUBERCULOSIS OF CHILDREN ADMITTED FOR CLINICAL EVALUATION BECAUSE OF EVIDENCED CONTACT (GROUP A) OR BECAUSE OF INDICATIVE CLINICAL SIGNS AND SYMPTOMS (GROUP B)

	Family	Other	All
Group A	129	13	142
Group B	16	28	44
All	145	41	186

χ^2=58.023, df=1, p<0.0001

TABLE 4
BACTERIOLOGICALLY POSITIVE CONTACTS WITH TUBERCULOSIS OF CHILDREN ADMITTED FOR CLINICAL EVALUATION BECAUSE OF EVIDENCED CONTACT (GROUP A) OR BECAUSE OF INDICATIVE SIGNS AND SYMPTOMS (GROUP B)

Source	Group A	Group B
Father	29	1
Mother	15	1
Grandfather	16	2
Grandmother	10	2
Brother or sister	8	0
Relative	20	0
Neighbour	9	1
Total	107	7

60 (22.1%), primary lung tuberculosis 49 (18.0%), early postprimary tuberculosis 4 (1.5%) and late postprimary tuberculosis 4 (1.5%).

As seen in Table 1, contacts were allocated within the family for 129 of 142 (90.8%) children admitted for clinical evaluation because of evidenced contact with tuberculosis (group A). There were 80 evidenced contacts with one or both parents (56,3%), 45 with one or both grandparents (31.7%) and 4 with siblings (2,8%). Relatives, neighbors, friends or schoolmates accounted for 13 known contacts (10.2%).

TABLE 5
AGE DISTRIBUTION OF CHILDREN HAVING IDENTIFIED CONTACTS WITH TUBERCULOSIS. COMPARISON OF CHILDREN ADMITTED BECAUSE OF *A PRIORI* EVIDENCED CONTACT WITH TUBERCULOSIS (GROUP A) AND CHILDREN ADMITTED BECAUSE OF SUSPECTFUL CLINICAL SIGNS AND SYMPTOMS (GROUP B)

Group	Years of age				
	0–4	5–9	10–14	15–19	All
A	37	56	40	9	142
B	10	12	17	5	44
All	47	68	57	14	186

χ^2=3.385, df=3, p=0.2799

In the group of 129 children admitted because of signs and symptoms arousing clinical suspicion of tuberculosis (group B), contacts with tuberculosis were identified for 44 children (34.1%, Table 2). There were 5 identified contacts with one or both parents (11.4%), 10 with one or both grandparents (22.7%), and 1 with siblings (2.3%). Relatives, neighbours, friends and schoolmates accounted for 28 of 44 identified contacts (63.6%). Thus, in contrast to group A, in which 90.8% of known contacts were within the family circle (including the grandparents) more contacts of the group B children were identified outside the family. The difference is statistically significant (Table 3, χ^2=58.023, df=1, p<0.0001).

Contacts with bacteriologically (BK) positive tuberculosis were identified for 107 of 142 children in group A (75.4%) and for 7 of 44 identified contacts of the children in group B (15.9%, Table 4).

Among the subjects who have had known contacts with tuberculosis (group A) there were more children 0–5 years of age (37 of 142, 26.1%) and 5–9 years of age (56 of 142, 39.4%), together 65.5%. Among the subjects admitted because of clinical suspicion at tuberculosis (group B) there was a small preponderance of identified

TABLE 6
AGE DISTRIBUTION OF CHILDREN HAVING IDENTIFIED CONTACT WITH TUBERCULOSIS. COMPARISON OF CHILDREN ADMITTED BECAUSE OF EVIDENCED CONTACT WITH TUBERCULOSIS (GROUP A) AND CHILDREN ADMITTED BECAUSE OF SUSPECTFUL CLINICAL SIGNS AND SYMPTOMS (GROUP B). COMPRESSED DATA FROM TABLE 4

Group	Years of age		
	0–9	10–18	All
A	93	49	142
B	22	22	44
All	115	71	286

χ^2=3.416, df=1, p=0.0646

contacts for the children 10–14 years of age (17 of 44, 38.6%), but the proportion of children in the two older age groups (10–14 and 15–18) was equal to the proportion of children in the two younger age groups (0–5 and 5–9), i.e. 22 of 44 in each (50.0%). Comparison of groups A and B with regard to the distribution into the four age groups (Tables 5 and 6) does not reach statistical significance (χ^2=3.835 df=3 p=0.279).

Discussion

Thus, contacts with possible source(s) of infection were identified for 186 of 271 (68.3%) of children 0–18 years of age referred to our hospital for clinical evaluation of possible tuberculosis. Similar experience has been reported five years ago by Croatian colleagues[7] and similar proportions have been found in populations with comparable incidence of tuberculosis, e.g. in Spain,[8–11] Italy[12], Poland[13] and Czech Republic[14]. A multistate survey in USA also yielded comparable results[15]. In a study involving 164 Californian children up to 15 years of age (92% of whom were either black, Hispanic or Asian) source cases were identified for 38% of the patients[8]. A study carried out in the megalopolis of New York City identified the sources for 21.3% of children below 5 years of age who have had tuberculosis[16].

In 129 of 142 children (90.8%) admitted to our pediatric pulmonary service because of known contact with tuberculosis (group A), the contact was allocated *within* the family circle. On the other hand, in 44 of 129 children admitted because of clinical suspicion at tuberculosis (group B) for whom it was possible to identify the contact, the contact was more often allocated *outside* the family (28 of 44 identified cases, 63.6%). High proportion of unrecognized contacts in that group (85 of 129, 65.9%) opens the possibility that extra-familial exposure to tuberculosis occurs even more commonly. Since children with tuberculosis are indicators of the prevalence of tuberculosis in population, our findings imply existence of a significant number of concealed cases of tuberculosis in the community.

Our study was a retrospective one and did not distinguish between sources of infection, possible sources of infection and case contacts since the data regarding the bacteriological positivity of the contacts of children in group B (admitted because of clinical suspicion) were scarce and incomplete. Additional epidemiological effort is needed to acquire more reliable data. Cluster investigations by means of molecular epidemiology may aid conventional epidemiological methods in identifing patients who had recently acquired tuberculosis and allow discrimination between transmitters and nontransmitters[17,18]. Molecular techniques were available to us in a limited extent.

Approximately 15% of the children involved in the present study were referred to our pediatric pulmonary service because of the PPD skin test conversion. Although BCG vaccination is obligatory in Croatia and 97% of children receive it, PPD skin testing may be a useful indicator of contact with tuberculosis if the child did not receive BCG within two years prior to the testing. In a recent case control study involving 96 children 1–5 years of age with PPD skin test $\supseteq$ 10 mm and normal chest radiograph, predictors of the skin test positivity were: contact with an adult having active tuberculosis or with a relative having positive skin test[16].

Identifiable contacts with tuberculosis were expected to obtain more often in younger children than in the older ones and adolescents, in view of the range of social contacts. That assumption was correct for the children admitted because of known contacts with tuberculosis (A), 65.5% of whom (93 of 142) were below 9 years of age. In the group of children admitted because of clinical suspicion at tuberculosis (B), however, identified contacts below and above that age limit were equal, i.e. 22 in children 0–9 years of age and 22 in children 10–18 years of age (50.0% each). That finding implies the need for additional efforts directed toward identification of tuberculosis among persons coming into close contacts with young children who present with signs and symptoms arousing clinical suspicion of tuberculosis.

Infection with *Mycobycterium tuberculosis* was bacteriologically verified in 17 of 117 children with clinical diagnoses of tuberculosis (14.5%). That is comparable to usual pediatric experience[3,7,19]. Using fingerprint matching of strains isolated from the index cases and from the incriminated source cases, Schaaf et al.[20] found that in 7 of 19 cases of infection within families the strains isolated from the index cases and the incriminated source cases were not identical, and conclude that the presence of an adult with infectious tuberculosis in the same household as a child with tuberculosis does not necessarily imply adult-to-child transmission.

In conclusion, 129 of 142 children (90.8%) children referred to our pediatric pulmonary service because of known contact with tuberculosis were usually exposed to tuberculosis within the family circle. On the other hand, contacts with tuberculosis were identified for only 44 of 129 children (34.1%) referred because of signs and symptoms arousing clinical suspicion of tuberculosis. Among these 44 identified contacts, 28 (63.6%) were allocated outside the family. Low proportion of unrecog-

nized contacts in that group (85 of 129, 65.9%) opens the possibility that extra-familial exposure to tuberculosis occurs more commonly. Recognized tuberculosis in children indicates presence of unrecognized tuberculosis in their social environment. Diligent and pro-active search aimed at their identification is desirable, particularly in populations at a high risk of tuberculosis, such as immunocompromised children and underpriviledged ethnic minorities.

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IZVORI INFEKCIJE TUBERKULOZOM U DJECE NA PODRUČJU ISTOČNE HRVATSKE

SAŽETAK

U retrospektivnom epidemiološkom istraživanju koje je provedeno u sjeveroistočnom području Hrvatske nastojalo se utvrditi moguće izvore infekcije tuberkulozom u dječjoj dobi. U tom je području zabilježen vidan porast incidencije tuberkuloze u djece poslije ratnih zbivanja 1991–1995. Tijekom deset godina (1993–2003) na bolnički je tretman upućeno 271 dijete u dobi do 18 godina bilo zbog poznatog kontakta s bolesnikom od tuberkuloze (142 djece, skupina A), bilo zbog kliničkih simptoma i znakova koji su u liječnika primarne zdravstvene zaštite pobudili sumnju na tuberkulozu (129 djece, skupina B). Mogući izvori infekcije utvrđeni su na temelju medicinske dokumentacije i terenskog istraživanja. Djeca skupine A bila su izložena infekciji tuberkulozom najčešće u krugu obitelji tj. u kontaktu s roditeljima, djedom ili bakom i braćom ili sestrama (129 od 142 djece, 90,8%). U krugu rođaka, susjeda, prijatelja ili suučenika identificirano je 9,2% kontakata s tuberkulozom. U skupini B mogući izvori infekcije identificirani su za 44 od 129 djece (34,1%), a od tih je 16 bilo u krugu obitelji (36,4%). Kontakt s tuberkulozom identificiran je u skupini A pretežno u mlađe djece (0–9 godina, 65,5%), a u skupini B kontakti su identificirani za podjednake postotke mlađih i starijih ispitanika – po 50,0% za dob 0–9 godina i za dob 10–18 godina. Visok postotak neprepoznatih izvora infekcije tuberkulozom u djece s kliničkim simptomima i znakovima tuberkuloze (skupina B, 85 od 129, 65,9%) upućuje na pretpostavku da se izlaganje infekciji tuberkulozom izvan obitelji događa češće nego što bi se moglo očekivati s obzirom na dob djeteta.